REMARKS

Summary of Office Action

As an initial matter, Applicants note with appreciation that the Examiner has indicated consideration of the Information Disclosure Statements filed October 15, 2004, May 16, 2005, February 7, 2006 and October 27, 2006 by returning signed and initialed copies of the forms PTO-1449 submitted therein.

Applicants note that the Restriction and Election of Species Requirements have been made final and claims 25, 26 and 39-67 have been withdrawn from consideration.

Claims 1-24, 27-38 and 68-74 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims of co-pending application Nos. 10/798,884, 10/910,806, 10/939,351, 11/012,267, 11/115,321, 11/102,725, 11/102,726 and 11/115,293.

Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA") in view of Findlay et al., U.S. Patent No. 4,650,807 (hereafter "FINDLAY").

Claims 1-24, 27-38 and 68-74 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA") in view of Paradissis et al., U.S. Patent No. 5,445,829 (hereafter "PARADISSIS").

Response to Office Action

Reconsideration and withdrawal of the rejections of record are respectfully requested in view of the following remarks.

Response to Provisional Rejection of Claims on the Ground of Non-Statutory Obviousness-Type Double Patenting

All claims under consideration are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims of co-pending application Nos. 10/798,884, 10/910,806, 10/939,351, 11/012,267, 11/115,321, 11/102,725, 11/102,726 and 11/115,293

Applicants respectfully request that these rejections be held in abeyance until the Examiner has indicated allowable subject matter. Applicants will then decide if the filing of one or more Terminal Disclaimers is warranted.

Response to Rejection of Claims under 35 U.S.C. § 103(a) over FANARA in View of FINDLAY

Claims 1-24, 27-38 and 68-74, i.e., all claims under consideration, are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of FINDLAY. The rejection essentially alleges that FANARA at least inherently discloses all of the elements of the rejected claims with the exception of explicitly disclosing promethazine and chlorpheniramine as antihistamines and guaifenesin as antitussive-expectorant. In particular, regarding the recitation of "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the

dosage form provides a plasma concentration within a therapeutic range of the first drug" in, e.g., claim 1 the Examiner takes the position that FANARA discloses this element, arguing that FANARA "explicitly recognizes and teaches simultaneous administration of multiple active agents whereby it is possible to combine therapeutic effects of active substances having very different pharmacokinetic profiles. Thus, the Fanara reference teaches an objective similar to that claimed by Applicant". Page 14, first paragraph of the present Office Action.

Regarding the plasma half-lives recited in the present claims, the rejection alleges that "the Fanara reference teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant." Page 14, second paragraph of the present Office Action.

Regarding the recitation of "the tablet comprises a matrix which comprises the first drug and has dispersed therein particles which comprise the at least one second drug" in e.g., present claim 21, the rejection alleges that FANARA "teaches the use of layered, both bi-layered and multi-layered tablets and thus, this limitation is also met by the primary reference." Page 14, third paragraph of the present Office Action.

With respect to FINDLAY, the rejection alleges that this document teaches antihistaminic compositions which can be in the form of tablets and also teaches pheniramines and promethazine as suitable antihistamines. The rejection further asserts that FINDLAY teaches that the active compound may be formulated with a sympathomimetic agent such as decongestants, an antitussive, an analgesic, anti-inflammatory or an antitussive expectorant, and that it would allegedly have been obvious to one of ordinary skill in the art to incorporate the suitable antihistamines and expectorants allegedly taught by FINDLAY within the formulations of FANARA.

Applicants respectfully traverse this rejection. In particular, it is pointed out that FANARA is primarily concerned with pharmaceutical compositions for the controlled release of active substances (see, e.g., title of FANARA), not with the simultaneous administration of different active substances and for this reason alone, one of ordinary skill in the art has no particular reason to consult FANARA for guidance in the latter respect.

The passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states:

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance. In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

The above passage is to be considered in combination with the passage from col. 5, line 39 to col. 6, line 26 of FANARA (emphasis added):

> According to a specific embodiment of the invention, the controlled-release pharmaceutical compositions according to the invention are used in combination with one or more pharmaceutical compositions allowing immediate release of active substances. When these two types of compositions are present in the same unit, this makes it possible to obtain, in a single administration, both the immediate release of a first active substance and the prolonged release of the same or of a second active substance.
>
> Accordingly, the present invention also relates to pharmaceutical compositions which can be administered orally, comprising
>
> A. at least one layer comprising an active substance and excipients which allow immediate release of the said active substance after administration, and
> B. at least a second layer which allows the controlled release of the same or of a second active substance, comprising the said same or second active substance, at least one matrix-type excipient and at least one alkalinizing agent.
>
> [...]
>
> Such combined pharmaceutical compositions can be prepared according to various

methods known to persons skilled in the art.

More particularly, these combined pharmaceutical compositions may be provided in the form of a tablet in which at least one layer A is stuck to at least one layer B.

[...]

The multilayer tablets are particularly well suited to cases of combinations of active substances for which very specific beneficial therapeutic effects have recently been obtained, for example, pseudoephedrine/cetirizine, hydrocodone/acetaminophen, immediate release hydrocodone/prolonged release hydrocodone.

The embodiments referred to by FANARA in the last paragraph of the above passage are illustrated in Example 4 (double-layer tablet containing controlled-release pseudoephedrine and immediate release cetirizine) and Example 7 (double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer).

Nothing in the above passages (or any other passage) of FANARA points in the direction of a dosage form which provides a plasma concentration within a therapeutic range of a first active substance and a plasma concentration within a therapeutic range of a second active substance over similar or substantially coextensive periods of time, respectively. Specifically, FANARA mentions exclusively immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances (in this regard, see also Table 10 in col. 10 of FANARA which lists the time-dependent release of the drugs in the double-layer tablet of Example 4), but is completely silent with respect to the duration of action of the active substances, let alone the duration of action of one drug in relation to the duration of action of the other drug. Moreover, the above underlined passage indicates that the immediate release/controlled release combinations of FANARA are not particularly useful in general but only for cases where "very specific beneficial therapeutic effects" can be obtained by administering two active substances in one dosage form.

Further, the present rejection relies on the fact that FANARA mentions that "[i]n the case

where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles". However, only with hindsight is it possible to conclude therefrom that the plasma concentrations of the two active substances should be in a therapeutic range over similar or substantially coextensive periods of time. In this regard, it is pointed out that the term "pharmacokinetic profile" encompasses a wide range of properties of a drug.

For example, according to

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

the term "pharmacokinetic profile" is defined as "The characteristics of a drug that determine its absorption, distribution and elimination in the body" (see ANNEX). Accordingly, it is not seen that the fact that FANARA mentions that an immediate release/controlled release combination makes it possible to obtain combined therapeutic effects by means of two active substances having very different absorption, distribution and elimination in the body renders it obvious to one of ordinary skill in the art to use a corresponding combination in order to provide a dosage form which provides plasma concentrations in a therapeutic range of these two active substances over similar or substantially coextensive periods of time.

Applicants further point out that the Examiner has failed to provide any (written or other) evidence which shows that differences in release rates of different active substances from a single dosage form result in and/or are conventionally used to provide plasma concentrations in a therapeutic range of two active substances which are present in the single dosage form over similar or substantially coextensive periods of time. In fact, the Examiner has not even cited to a single

example of the use of different release rates (and in particular, a combination of immediate release and controlled release) for achieving similar or substantially coextensive periods of therapeutic activity of two different active substances, let alone of two different active substances which comprise promethazine and/or a pharmaceutically acceptable salt thereof.

In other words, even if one were to agree, *arguendo*, with the Examiner that FANARA "teaches an objective similar to that being claimed by Applicant" Applicants are unable to see that this renders obvious the recitation "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug" in, e.g., present claim 1, let alone in combination with the fact that the first drug is promethazine and/or a pharmaceutically acceptable salt thereof, i.e., a drug which is not even mentioned in FANARA.

Applicants also respectfully disagree with the Examiner regarding the assertion that FANARA "teaches similar active ingredients as claimed and thus, the plasma half-lives would be expected to be the same as that claimed herein by Applicant." Specifically, as set forth in, e.g., paragraphs [0002] and [0044] of the present specification, a single dose of promethazine hydrochloride can provide a therapeutically effective plasma concentration for an extended period of time, up to 12 hours and even longer, whereas a single dose of an expectorant such as guaifenesin will usually provide relief for only about one hour, and decongestants, antitussives, and analgesics usually provide relief for about 4 to 8 hours per single dose. Further,the period over which the therapeutic range of a particular drug may be provided in a given case depends, at least in part, on the plasma half-life of the drug and/or active metabolites thereof. The shorter the plasma half-life of a

particular drug, the shorter will be the period within the therapeutic range of the drug which is provided by a single administered dose of the drug. In other words, it is not seen that FANARA teaches drugs with a (relatively long) plasma half-life similar to that of promethazine, let alone in combination with one or more drugs with considerably shorter plasma half-lives than that of promethazine.

Further, Applicants also fail to see why a (bi- or multi-)layered tablet allegedly is the same as a tablet comprising a matrix which comprises a drug and has dispersed therein particles which comprise a second drug as apparently alleged at page 14, third paragraph of the present Office Action, and neither has the Examiner provided any explanation in this regard.

Regarding FINDLAY, Applicants respectfully submit that contrary to what is asserted in the last paragraph of page 14 of the present Office Action, this document does not teach that suitable antihistamines for the composition disclosed therein include pheniramines and promethazine. In this regard, the Examiner's attention is directed particularly to col. 1, lines 27-39 of FINDLAY where it is stated (emphases added):

> The antihistamines now in use, eg. diphenhydramine, pheniramines, pyrilamine, promethazine and triprolidine, exhibit varying degrees of anticholinergic activity. Such activity causes dryness of mouth, blurred vision and tachycardia and is generally regarded as undesirable.
>
> A novel compound having potent antihistamine activity which is substantially free from sedative effects, and which has little or no anticholinergic effect has now been discovered.
>
> Accordingly this invention provides the compound of formula (I), which is named (E)-3-{6-[3-Pyrrolidino-1-(4-tolyl)prop-1E-enyl]-2-pyridyl}acrylic acid.

Accordingly, even if one were to assume, *arguendo*, that one or ordinary skill in the art would be motivated to combine the teachings of FANARA and FINDLAY, the latter document would provide a disincentive rather than a motivation to include an antihistamine such as promethazine in

one of the compositions disclosed by the former document. This is yet another reason why even a combination of the teachings of FANARA and FINDLAY is unable to render obvious the subject matter of any of the present claims.

At any rate, FINDLAY is unable to cure the deficiencies of FANARA set forth above and in particular, fails to renders it obvious to one of ordinary skill in the art to provide a dosage form which comprises (any) two different active substances and provides similar or substantially coextensive periods of therapeutic activity of these two different active substances.

Applicants submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of any of the present claims in view of FANARA and FINDLAY. Accordingly, the rejection of claims 1-24, 27-38 and 68-74 under 35 U.S.C. § 103(a) over FANARA in view of FINDLAY is without merit and should be withdrawn, which action is respectfully requested.

Response to Rejection of Claims under 35 U.S.C. § 103(a) over FANARA in View of PARADISSIS

Claims 1-24, 27-38 and 68-74 are also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over FANARA in view of PARADISSIS. The Examiner's arguments with respect to FANARA appear to be the same as those set forth in connection with the rejection of these claims over FANARA in view of FINDLAY (discussed above).

Regarding PARADISSIS the rejection alleges that this document teaches extended release pharmaceutical compositions (preferably in the form of a tablet) containing both an immediate release formulation and an extended release formulation and that the compositions include

pharmaceutically active compounds, such as antihistamines (suitable examples whereof allegedly include chlorpheniramine maleate and promethazine), antitussives, expectorants and decongestants (suitable antitussive-expectorants allegedly include guaifenesin). The rejection further asserts that it would allegedly have been obvious for one of ordinary skill in the art "to incorporate the suitable antihistamines and antitussive-expectorants taught by Paradissis et al. within the formulations of Fanara et al."

This rejection is respectfully traversed as well. Specifically, PARADISSIS, like FANARA and FINDLAY, is unable to render it obvious to one of ordinary skill in the art to provide a dosage form which comprises (any) two different active substances and provides similar or substantially coextensive periods of therapeutic activity of these two different active substances.

Further, PARADISSIS fails to provide any motivation for one of ordinary skill in the art to employ promethazine, i.e., a drug which is mentioned in the laundry list of exemplary substances which can be incorporated in the pharmaceutical formulations disclosed therein (see col. 4, lines 31-64 of PARADISSIS) and which is not included in the list of preferred drugs in the paragraph bridging columns 4 and 5 of this document, in combination with any of the other exemplary drugs mentioned in PARADISSIS, let alone in a form which provides similar or substantially coextensive periods of therapeutic activity of promethazine and the other drug(s).

It is noted that in two of the Examples of PARADISSIS combinations of drugs are employed. Specifically, Example 2 describes an extended release capsule containing pseudoephedrine hydrochloride and chlorpheniramine maleate and Example 3 describes extended release capsules containing phenylpropanolamine hydrochloride and chlorpheniramine maleate. Both of these capsules comprise immediate release particles and extended release particles. However, in both of

these Examples the active ingredients are blended together prior to being formulated into the particles (see, e.g., col. 11, lines 16-20 and 64-68 of PARADISSIS) and thus, they are both present in the immediate release particles as well as in the extended release particles. In view thereof, it is to be expected that both drugs have very similar release (dissolution) profiles (see tables in col. 11, lines 40-48 and col. 12, lines 21-28).

Even if one were to assume, *arguendo*, that one of ordinary skill in the art would be motivated to replace the chlorpheniramine maleate of Examples 2 and 3 of PARADISSIS with promethazine and/or a pharmaceutically salt thereof, this would not render obvious any of the claimed subject matter because, as set forth above and in the present specification, promethazine can provide a therapeutically effective plasma concentration for an extended period of time, up to 12 hours and even longer, and it is apparent that a dosage form which comprises promethazine in an extended release formulation will even prolong this period rather then shorten it to better match it with the duration of the action of any other drugs combined therewith.

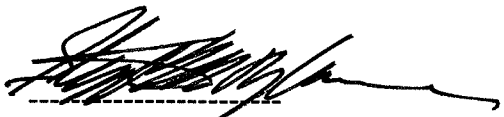
In view of the foregoing, it is submitted that even in combination with PARADISSIS, FANARA is unable to render obvious the subject matter of any of the present claims, wherefore withdrawal of the rejection of claims 1-24, 27-38 and 68-74 under 35 U.S.C. § 103(a) over FANARA in view of PARADISSIS is warranted as well and respectfully requested.

CONCLUSION

In view of the foregoing, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested. If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to contact the undersigned

at the telephone number below.

Respectfully submitted,
Viswanathan SRINIVASAN et al.



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ANNEX

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Glossary

β-DYSTROGLYCAN The α- and β-dystroglycans are the laminin-binding components of the dystrophin–glycoprotein complex, which provides a linkage between the subsarcolemmal cytoskeleton and the extracellular matrix.

ACETYLCHOLINE A neurotransmitter ($C_7H_{17}NO_3$) that is released at autonomic synapses and neuromuscular junctions. It is active in the transmission of nerve impulses and is formed enzymatically in tissues from choline.

AMINOGLYCOSIDES A group of antibiotics (such as gentamicin) that inhibit bacterial protein synthesis and are particularly active against Gram-negative bacteria.

CYTOTOXICITY The properties of a virus, transgene, vector, compound or molecule that are toxic for cells.

CpG ISLAND Genomic regions that are rich in the CpG pattern, are resistant to methylation and are often associated with promoter activity.

DEPENDOVIRUS A single-stranded DNA virus from the family parvoviridae (subfamily parvovirinae), which is dependent on a co-infection with helper adenoviruses or herpes viruses for efficient replication.

DYSTROBREVINS The components of the dystrophin–glycoprotein complex that bind to syntrophin and (indirectly) to the C-terminal of dystrophin. Dystrobrevin-α recruits signalling proteins, such as neuronal nitric oxide synthase.

ELECTROPORATION The application of an electric current to the plasma membrane of a cell, to temporarily open pores or channels through which DNA might pass.

EPISOMES DNA that can replicate autonomously in the cytoplasm of host cells.

EXTRACELLULAR MATRIX In muscle, this is a thin layer (basal lamina) that contains collagen, elastin and fibronectin, which surrounds each muscle fibre. This might act as a semipermeable filter or a selective cellular barrier and is important in regeneration after damage.

F-ACTIN A protein that is involved in the contractile apparatus and the maintenance of the cytoskeleton of myofibres.

HEK-293 CELLS Host cells that generate viral particles following transfection with the rAAV plasmid and the helper plasmid.

IMMUNOGENICITY The properties of a virus, transgene, vector, compound or molecule that provoke an immune response.

MICROBUBBLES Encapsulated gas microbubbles that can be used as drug or gene carriers, which are able to penetrate into the smallest membranes. When exposed to sufficiently high-amplitude ultrasound, the microbubbles rupture and release the drugs and genes that are contained in their encapsulating layer.

MYOBLAST TRANSPLANTATION The implantation of exogenous muscle-progenitor cells into muscle to generate new myofibres or to support existing myofibres.

NEO-ANTIGEN A foreign (transgene) product that is able to stimulate an immune response.

PHARMACOKINETIC PROFILE The characteristics of a drug that determine its absorption, distribution and elimination in the body.

PRE-mRNA SPLICING The removal of introns from the precursor mRNA molecule; the remaining exons are spliced together.

PRESSURIZED ISOLATED-LIMB PERFUSION The introduction of therapeutic agents under pressure in a limb after isolation of the blood circulation by clamping.

PRIMARY MUSCLE-CELL CULTURES Cells that are taken into culture directly from a tissue biopsy. In contrast to cell lines that only contain immortalized cells, these cultures contain heterogeneous cell populations.

RNaseH Ribonuclease H. An enzyme that cleaves RNA/DNA complexes.

SARCOLEMMA The membrane that encloses a striated muscle fibre.

SPECTRIN A large contractile submembrane protein that, similar to dystrophin, contains an actin-binding domain and a long repeat domain.

SPLICEOSOMAL COMPLEX A large dynamic complex that consists of small nuclear RNA molecules and protein components. It mediates the two catalytic steps of the splicing reaction: the excision of introns from the pre-mRNA and the ligation of the two exon termini.

SYNTROPHINS Peripheral membrane proteins that bind to the C-terminal of dystrophin, which might have a role in the process of synaptogenesis.

TRANSDUCTION The transfer of genetic material into a cell using a viral vector.

TRANSFECTION The transfer of exogenous DNA into a cell.